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**Case Report**

# From heart to brain: a rare thrombotic presentation in homocystinuria - a case report

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## ABSTRACT

Homocystinuria is an uncommon autosomal recessive metabolic disorder caused by cystathionine β-synthase (CBS) deficiency, leading to impaired methionine metabolism and elevated homocysteine levels. The disorder presents with multisystem involvement, including neurocognitive deficits, lens dislocation (ectopia lentis), skeletal deformities such as osteoporosis, and a significant predisposition to thromboembolic phenomena, including deep vein thrombosis, sagittal sinus thrombosis, and myocardial infarction. Cerebral sinovenous thrombosis (CSVT), though rare, is a potentially life-threatening cerebrovascular event in children, often linked to risk factors such as dehydration, infection, trauma, malignancies, or underlying thrombophilias. While homocystinuria more commonly results in arterial strokes, CSVT as an initial clinical manifestation is exceedingly rare. Here, we present the case of an 8-year-old girl in whom CSVT was the first indicator of undiagnosed homocystinuria.

**Keywords:** Cerebral sinovenous thrombosis, Homocystinuria, Thrombophilias

## INTRODUCTION

Cerebral sinovenous thrombosis (CSVT) represents an uncommon but significant etiology of pediatric stroke, with an incidence estimated at around 1 in 100,000 children annually. It accounts for up to one-quarter of all ischemic stroke events in the pediatric population.[1] The condition arises due to thrombotic obstruction of the cerebral venous sinuses, resulting in increased venous pressure. This pressure build up may be restricted to a specific venous territory or cause diffuse intracranial hypertension.[2]

CSVT often has a gradual onset, with clinical signs that are frequently vague and non-specific. In contrast to arterial strokes, which typically produce sudden-onset focal deficits, CSVT tends to present with more generalized or evolving neurological features over a span of hours to several days or weeks.[3] Key symptoms include headache, vomiting, altered consciousness, and signs of raised intracranial pressure such as papilledema and cranial nerve VI palsy. Seizures are also more frequently observed in CSVT than in arterial ischemic events. In neonates and infants, the clinical picture often centers around nonspecific encephalopathy and seizures, with limited localizing neurological findings.[4]

## CASE REPORT

An 8-years-old female child, born of a non-consanguineous marriage, was admitted with complaints of headache and neck rigidity for 4 days, and fever for 1 day. She was the fourth female child, born via normal vaginal delivery, and was developmentally normal. There was no history of bleeding tendency in the family. She was conscious, alert, and afebrile. Signs of meningeal irritation were positive, and signs of raised intracranial pressure were noted. There was a history of ocular surgery of the right eye for lens dislocation 1 month before presenting to our hospital. On fundoscopic examination, grade 3 papilledema was diagnosed by direct ophthalmoscopy, hence, she was started on 3%

sodium chloride infusion. In the laboratory investigations, apart from leucocytosis (WBC: 15,270 and PMN: 84.8%), other routine laboratory parameters, including coagulation profiles, were all within normal limits. MRI of the brain revealed absence of normal flow voids in the superior sagittal sinus, right transverse sinus, and right sigmoid sinus, all of which appeared dilated.

T1-weighted sequences demonstrated hyperintense signals, while T2-weighted images were isointense with evidence of blooming on gradient echo imaging features consistent with cortical venous sinus thrombosis (Figure 1). Post-contrast images highlighted multiple intraluminal filling defects. Additional findings included an empty sella and subtle leptomeningeal enhancement in the right parieto-occipital region, raising suspicion for concurrent meningitis (Figure 2).

High-resolution CT of the temporal bones confirmed right-sided mastoiditis. A lumbar puncture was performed but was traumatic. The child was started on intravenous Ceftriaxone, Levetiracetam, Enoxaparin (0.5 mg/kg/dose every 12 hourly subcutaneous) and symptomatic treatment. Fasting plasma homocysteine was 356 µmol/l, and vitamin B12 levels were reduced (132 pg/ml). Based on these findings, a provisional diagnosis of homocystinuria was established. The child was started on pyridoxine, folic acid, and vitamin B12 supplementation.

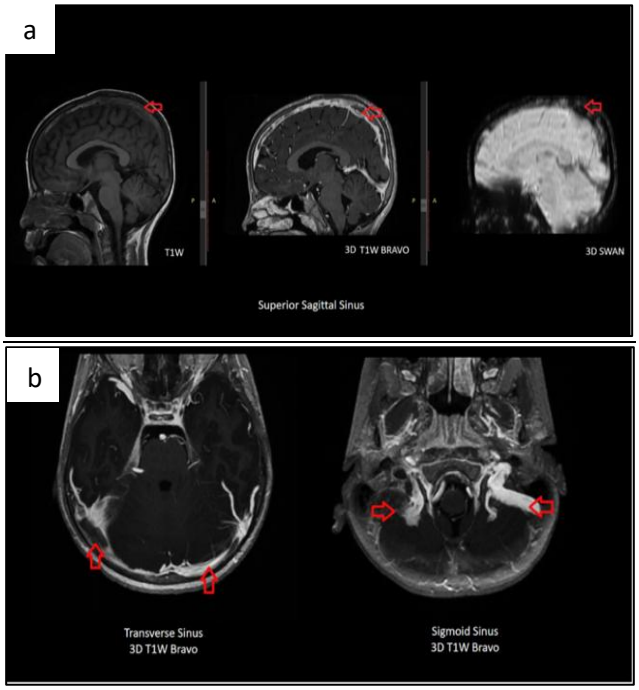


**Figure 1 (a and b): MRI brain (plain and contrast) of the patient demonstrating loss of flow void and distension of the superior sagittal, right transverse, and right sigmoid sinuses. T1 hyperintense, T2 isointense signals with blooming on gradient images and post-contrast filling defects are suggestive of cortical venous sinus thrombosis.**

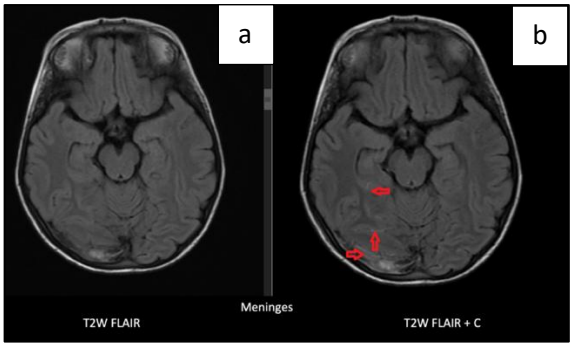


**Figure 2 (a and b): Mild leptomeningeal enhancement is right parieto-occipital lobe, suggestive of meningitis.**

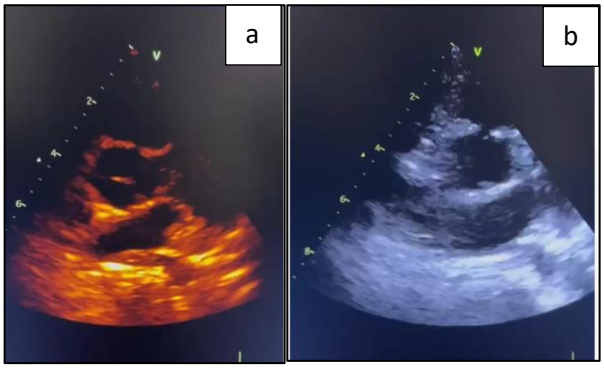


**Figure 3 (a and b): 2D echocardiogram image of a significant-sized thrombus located in the left atrial appendage.**

On day 5 of admission, the child complained of chest pain. A 2D echocardiogram was done, which revealed a substantial sized thrombus identified within the left atrial appendage, mild concentric left ventricle hypertrophy with trivial aortic regurgitation and good biventricular function following which tablet aspirin and rivaroxaban were added to the treatment. Genetic testing confirmed the diagnosis, revealing a homozygous c.346G>A (p.Gly116Arg) mutation in exon 5 of the CBS gene (transcript ENST00000398165.8). This variant is associated with Homocystinuria (OMIM 236200), a metabolic disorder that may or may not respond to pyridoxine therapy. The condition follows an autosomal recessive inheritance pattern. Based on established classification criteria (PS3, PS4, PP3, PP5), the variant is considered pathogenic. The child was discharged in stable condition with no active complaints.

## DISCUSSION

Homocystinuria is a rare autosomal recessive metabolic disorder that disrupts the normal metabolic processing of methionine, resulting in elevated levels of homocysteine and its metabolites in blood and urine. The classical form stems from deficient or absent activity of cystathionine β-synthase (CBS), impairing the transsulfuration pathway by blocking the conversion of homocysteine to cystathionine, and thus interfering with its remethylation

to methionine.[1] Affected neonates are typically asymptomatic at birth, and early clinical features such as failure to thrive or developmental delay may be subtle and easily overlooked in infancy.[2] This disorder exerts a broad impact across multiple systems, including the central nervous, ocular, musculoskeletal, and vascular systems.[2] In children presenting with CSVT, both inherited and acquired prothrombotic conditions are commonly implicated. Notable risk factors include cranial infections, trauma, malignancies of hematologic origin, dehydration, and a variety of thrombophilic states.[2-4] Several hypercoagulable conditions are recognized contributors to pediatric CSVT. These include deficiencies of natural anticoagulants (e.g., protein C or S), factor V Leiden mutation, raised lipoprotein(a), antiphospholipid antibodies, and inherited metabolic disorders like homocystinuria.[3] Although infrequent, homocystinuria represents a treatable metabolic cause of thrombosis and should not be overlooked in thrombotic presentations.[3] Type I homocystinuria, due to CBS deficiency, is characterized by a constellation of clinical features: dislocation of the ocular lens (ectopia lentis), cognitive impairment, skeletal features resembling Marfan syndrome (e.g., tall stature, long limbs), and a propensity for thromboembolic events.[5]

Ocular manifestations, particularly ectopia lentis, typically emerge after three years of age and may be accompanied by high myopia or iridodonesis. In our patient, lens subluxation was noted at 8 years. Skeletal findings can include dolichostenomelia, scoliosis, a high-arched palate, pes cavus, and radiographic evidence of osteopenia or osteoporosis.[5] Neurological outcomes vary significantly, ranging from normal intellect to severe developmental delay. Thrombosis is a defining feature of homocystinuria and can involve vessels of any size at any age. While arterial ischemic stroke is a well-documented complication, cerebral sinovenous thrombosis as an initial clinical event remains uncommon in pediatric cases.[6-8]

## CONCLUSION

This case underscores the necessity of considering metabolic conditions like homocystinuria in children presenting with CSVT, particularly when accompanied by other suggestive features such as ectopia lentis. Prompt recognition, multidisciplinary management, and genetic testing can be life-saving and prevent irreversible sequelae.

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